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NUTRITION REVIEWS

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NUTRITION REVIEWS

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HEIGHTS AND WEIGHTS OF ADULTS IN THE UNITED STATES

Height-weight relationships are used as one criterion of nutriture, although many other measurements are also informative of physical well-being.

Data available to USDA have been summarized in a new bulletin (*Home Economics Research Report No. 10*, by Hathaway and Foard). Through the evaluation of published and unpublished height-weight data an attempt was made to provide as adequate a description as possible of our present population in the United States.

The report contains information on average heights and weights related to age, average weights for height and age, data on men in the military services, data from other countries compared with data from the United States, and changes in the United States population between 1790 and 1950. Also included is an addendum presenting two tables from the *Build and Blood Pressure Study of 1959*, published by the Society of Actuaries in 1959 as our bulletin was ready to go to press.

No comprehensive statistical study of measurements of men and women has been made in the United States. Height-weight standards in common use are based on data from the Association of Life Insurance Medical Directors and the Actuarial Society of America collected between 1885 and 1908 and first published in 1912. Since that time many more measurements have been made, most of them under more exacting conditions—without shoes or other clothing. Newer data have come primarily from studies based on reports from medical examinations for insurance policies, or were incidental to various studies on college students, on groups involved in food consumption surveys, or on men in the military services. In 1949–50, however, the American College Health Association brought together the measurements made on about 160,000 students entering 103 colleges in 34 states, and the U. S. Department of Agriculture tabulated them for this report, presenting a cross section of persons in this classification.

From all these studies certain generalizations can be drawn. Men born in the United States in the late 1920's are at least an inch taller than those born about 1900, who, in turn, are an inch taller than those born in the 1870's or 1880's. Men of 18 to 20 years now average as tall as or taller than those 20 to 30 years of age. The average height of men who have reached their maximum growth is now nearly 70 inches (without shoes) compared with about 69 inches around 1925, and 68 inches or less around 1900. Women, too, are taller than formerly, averaging 64.5 inches and over (without shoes) at 17 to 25 years in many of the recent studies, compared with 63.5 to 64.0 inches in the 1920's and 62.5 inches or less in the early 1900's.

Consecutive height-weight averages for students entering the older American colleges show similar increases. Men entering in the 1950's averaged about a year younger than those entering around 1900, but averaged 2 inches taller than 50 years before—70 instead of 68 inches. Perhaps even more striking is the percentage of young men who were at least 6 feet tall—in 1900 about 5 or 6 per cent, in the 1920's 10 to 15 per cent, and from 1955 to 1957 as high as 30 per cent. Weights of the men increased from about 134 to 158 pounds in the same

time period—slightly more than would be expected for 2 inches in height.

In similar studies on college women, the height averaged about 63.6 inches in 1900 and had increased to 65.2 inches by the 1950's. Average weights were about 120 pounds in 1900 and 127 pounds in the 1950's—about what would be expected for the increase in height.

Two types of special analyses—relation of stature and weight to urbanization and to the education of the homemaker—were possible with height-weight data from the USDA Household Food Consumption Survey of 1955. For the men in the United States, there were no consistent differences in heights or weights related to urbanization. However, urban women showed a tendency to be shorter and lighter and rural women taller and heavier than the other groups.

Height-weight data for men and women related to formal schooling of the homemaker showed direct relationship between heights and extent of education of the homemaker. The shortest adults were in households having homemakers with only elementary school education and the tallest in those households having homemakers with at least some college education. For the men the weights were generally in the same direction. Women in households in which the homemaker had only elementary school training were heavier, however, than the taller women in households in which the homemaker had some college training: for example, at 40 to 49 years of age the shorter women averaged 0.7 inch less and 17 pounds more than the taller ones.

The bulletin includes a number of tables of weights for height and age proposed by various investigators as standards. Tables showing distribution of weights for height and age by 10 pound intervals are also presented. An example of the trend in weight with age is illustrated by the data for college men 70 inches tall. At ages 17, 20–24, 30–39, and 40+ years, 47, 35, 27, and 17 per cent respectively weighed less than 150 pounds, and 9, 13, 21, and 31 per cent respectively weighed more than 180 pounds. For the college women 65 inches tall the percentages changed little until in the 40+ age group: 34 to 30 per cent weighed less than 120 pounds for the 17 through 39 year groups but only 10 per cent for the 40+ year group; about 10 per cent of the younger women weighed 150 pounds and over compared with 32 per cent of the older women.

Insurance companies, on the basis of mortality studies, advocate that weights at 20 to 30 years of age should not be exceeded as one grows older. In accord with this principle, a new table based on data from the American College Health Association study and reproduced here suggests desirable limits of weight for height for men and women of the United States. The range of weights suggested for men in this new table agree within a few pounds with the ranges for "desirable" weights for heights and body frame published by the Metropolitan Life Insurance Company (*Metro. Life Ins. Co. Stat. Bull.* **24,** *No. 6 (1943)*). The ranges suggested for women are six to 11 pounds lower than those in the older table (*Ibid* **23,** *No. 6 (1924)*), even with corrections for heel heights and weight of clothing. Corrected values of weight for height in the middle of their "medium" range correspond to the "high" values in the new tables. Use of standards of measurement without clothing have the advantage over measurements with shoes and other clothing that it is easier to correct for the weight of present-day clothing than to estimate such corrections for an indefinite time in the past.

Data available from records of men in the military services represent weights of healthy young men in various periods in our history. Analysis of such data shows that men in the armed services of World

*Weights for heights of men and women**

Height	Weights for Men			Weights for Women		
	Low	Median	High	Low	Median	High
Inches	*Pounds*	*Pounds*	*Pounds*	*Pounds*	*Pounds*	*Pounds*
60	—	—	—	100	109	118
61	—	—	—	104	112	121
62	—	—	—	107	115	125
63	(118)	(129)	(141)	110	118	128
64	(122)	(133)	(145)	113	122	132
65	126	137	149	116	125	135
66	130	142	155	120	129	139
67	134	147	161	123	132	142
68	139	151	166	126	136	146
69	143	155	170	130	140	151
70	147	159	174	133	144	156
71	150	163	178	(137)	(148)	(161)
72	154	167	183	(141)	(152)	(166)
73	158	171	188	—	—	—
74	162	175	192	—	—	—
75	165	178	195	—	—	—

Weights were based on those of college men 25 to 29 years old and college women 20 to 24 years old. Measurements were made without shoes and other clothing. The range from "low" to "high" at a given height included the middle 50 per cent of the cases. Half the weights were below the median and half above. Body build will determine where within the ranges given normal weight should be. Weight at any age probably should not vary from these values by more than five pounds for the shorter adults and ten pounds for the taller ones. Values in parentheses were extrapolated.

* From Home Economics Research Report No. 10, USDA.

War I were shorter than those of the Civil War or World War II. This difference was explained by the decrease in immigration of persons from Ireland and Germany after about 1890, and the increase of those of shorter stature from eastern and southern Europe. Since 1930 immigration has been largely curtailed so that the increase in size since then has been from other causes such as improved socioeconomic status of much of the population, improvement in medical care and sanitation, greater availability and consumption of nutritious foods, as well as improvement in the general knowledge of nutritional needs.

Data from other countries were compared briefly with data from the United States. Increase in stature over the years has been reported for Swedish and Norwegian men and women and for Danish men. Data for different age groups in Canada and Great Britain indicate increased heights in younger men and women. In the early 1950's, the men from the United States were the tallest, the Norwegians were nearly as tall, and the Canadians averaged from one to over two inches shorter than U. S. men at all ages. The Norwegian men were lighter and Canadian men heavier than U. S. men considering the differences in their height. The height and weight of the Norwegian and U. S. women averaged nearly the same, but the Canadian women were shorter and slightly lighter than those of the other two groups.

Data on sedentes, immigrants, and children of the immigrants born in the United States show that people of many nationalities grow taller in the United States than those in the homeland. A major difficulty in studies of growth and size is the separation of such factors as accelerated maturation and genetic diversification from serial changes produced by introduction of newer ethnic strains and the effects of the many environmental factors.

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IRON DEFICIENCY IN PREMATURELY BORN INFANTS

Late anemia of prematurity can be prevented by either oral or intramuscular iron.

Iron deficiency ranks as one of the most common handicaps to which the prematurely born infant is subject. The large majority of such infants will develop iron

deficiency anemia during the first year of life when fed the usual diet without supplemental iron. Consequently, a great deal of attention has been given the attempts to prevent this occurrence.

The duration of the anemia in such infants is an inverse function of gestational age (*Nutrition Reviews* **8,** *353* (*1950*)). Recently, T. R. C. Sisson and C. J. Lund (*Am. J. Clin. Nutrition* **6,** *376* (*1958*)) have shown that the adequacy of iron nutrition in the mother also has an important bearing on this question. Although these and other factors are operative here, the principal causative factor in this group of infants is undoubtedly their rapid rate of growth. A small prematurely born infant may easily weigh six times his birth weight at one year of age. Hence the need for an abundant intake of iron if the circulating hemoglobin mass is to keep pace with the increase in body weight.

It has long been customary to offer such infants supplemental iron in the form of ferrous salts, beginning in the second or third month of life. However, a number of clinicians, particularly those dealing with an indigent urban clientele, have been concerned that optimal results are not always obtained with such a regimen. Mothers may fail to offer the iron medication consistently or correctly, and attendance at well-baby clinics where instruction in feeding is given may be sporadic.

It is for these reasons that the potential usefulness of parenterally-administered iron preparations has been under intensive study in recent years. Following R. O. Wallerstein's report (*J. Am. Med. Assn.* **164,** *962* (*1957*)) of the parenteral use of iron-dextran in infants, a number of workers have evaluated this particular preparation which is marketed under the trade name of Imferon. There can be little doubt but that it is effective in the treatment of iron deficiency anemia in young infants.

Two recent articles report the use of intramuscularly administered iron-dextran in the prevention of iron deficiency anemia in prematurely born infants. J. James and M. Combes (*Pediatrics* **26,** *368* (*1960*)) report on 205 consecutively prematurely born infants who weighed 2,000 g. or less at birth and survived at least 24 hours. The infants were divided into two groups "by random selection," one group to receive iron-dextran, the other to serve as controls. Of the 181 infants who survived the neonatal period, 84 were in the treated group and 97 in the control group.

Provisions were made for close follow-up care of these infants; nonetheless, it was possible to observe firsthand only 38 per cent of the treated group for 11 months or more, and 51 per cent of the control group. It was felt that most of the defections were due to social and economic factors.

Iron-dextran was given in the nursery when the infant's weight reached 2,000 g. Five daily intramuscular injections provided a total dose of 250 mg. of elemental iron, a quantity calculated to provide the required amount for the first year of life. No supplemental iron was given to the control group except where severe anemia occurred. Milk formulas and solid food additions were presumably the same for both groups, though no specific statement is made by the authors on this point. The distribution of birth weights between the two groups of infants proved to be comparable, with one exception. For the smallest infants (birth weight less than 1,250 g.), 16 were in the control group and only eight in the treated group.

Results of this study indicate that iron-dextran injections given early in life are effective in preventing iron deficiency anemia, as judged by blood hemoglobin concentration (micro hematocrit determinations are said to have been done, but no data are given). Differences in hemoglobin concentration between the two groups first become manifest at age nine to ten weeks (10.5 g. per 100 ml. for treated versus 9.6 g. for control). By age 21 to 24 weeks these values

are 12.2 and 8.8 g. per 100 ml., respectively. At one year of age none of the treated infants had a blood hemoglobin below 9.3 g. (average 11.5 g.) whereas only five of the control infants (or 10 per cent of the total group followed) fell into this range, and 50 per cent of controls had values less than 7.5 g. per 100 ml. It would appear that therapy with iron-dextran resulted in normal hemoglobin values for most of these infants in contrast to a very high incidence of anemia in the controls.

A. L. Sitarz, J. A. Wolff, and F. H. Von Hofe (*Pediatrics* **26,** *375 (1960)*) report a similar type of study. The subjects were a group of 100 infants weighing less than 1,800 g. at birth. Alternate infants received intramuscular iron-dextran upon reaching a weight of 2,100 g., with control infants given *oral* ferrous sulfate. The dosage of iron-dextran was only about half that used by James and Combes. Difficulties were also encountered in making follow-up observations, since only 64 of the infants could be followed for nine months or longer. Comparisons were made with infants of comparable birth weight who were observed some years ago in the same clinic but who had not received supplemental iron.

Laboratory data included erythrocyte and reticulocyte counts, hemoglobin concentration, hematocrit, and the derived indices of mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Subjects were divided into birth weight groups in assessing the results.

In general, the results indicate that the responses to intramuscular iron and oral iron were quite similar and rather different from that seen in the group of untreated infants. For example, in the smallest infants (those weighing less than 1,200 g. at birth) hemoglobin values at nine to 12 months of age were as follows: oral iron—11.4 g. per 100 ml.; intramuscular iron—11.5 g.; untreated—7.7 g. Differences in erythrocyte counts were less pronounced, though in the same direction, as might be expected in iron deficiency. Reticulocyte counts tended to be higher in the untreated infants.

Erythrocyte indices were comparable in the infants of both treated groups, as were the hematocrit values. Unfortunately, these values were not available for the untreated group.

These two studies leave no doubt as to the effectiveness of intramuscular iron-dextran in preventing the late anemia of prematurity. This preparation is certainly as good as oral iron, and the authors of both papers emphasize its inherent value in the management of infants whose parents cannot be trusted to follow directions carefully—the lack of cooperation of such parents may result in sub-optimal therapy when daily medication is necessary.

In the face of these glowing results, other important aspects of the problem are brought out by the articles of James and Combes, and Sitarz *et al.*, and by a recent editorial by I. Schulman (*Pediatrics* **26,** *347 (1960)*). These are the evaluation of the need for supplemental iron (other than to prevent anemia) and the potential toxic effects from iron-dextran administration.

James and Combes, realizing that many of the prematurely born infants in their clinic suffered from intercurrent illness during infancy, undertook a clinical comparison of those infants who received iron and those who did not. As stated earlier, the latter group had blood hemoglobin values only two-thirds that of the former.

Interestingly enough, there was no difference in weight gains between anemic and nonanemic babies during the first year of life. Nor was there any difference in the incidence of respiratory tract or gastrointestinal tract infections. Frequency of hospital admission was the same. Five deaths occurred in the treated group; three in the controls. These observations certainly do not support the common clinical dictum that anemic infants are more prone to

intercurrent infections. This is not to say that iron deficiency anemia should be condoned; it merely points up the fact that evidences for malfunction in anemic infants should be sought in areas other than growth performance and susceptibility to infection.

At the very time these studies were being carried out, reports of possible toxicity from intramuscular iron-dextran were appearing in the literature. Schulman (*loc. cit.*) reviews this problem and comments on the general question of the toxicity of drugs and food additives with special reference to carcinogenesis. Two groups of workers (H. G. Richmond, *Brit. Med. J.* **1,** *947 (1959)* and A. Haddow and E. S. Horning, *J. Nat. Cancer Inst.* **24,** *109 (1960)*) found that *repeated* injections of *large* doses of iron-dextran *into the same site* resulted in an appreciable incidence of sarcomata at the injection site in both rats and mice. Injections of dextran alone produced no tumors. Moreover, tumors did not occur in Chinese hamsters, guinea pigs or rabbits given injections of iron-dextran.

These experiments represent extreme conditions unlikely to be duplicated in clinical practice. No reports of human malignancy have been made. Nevertheless, on the basis of these animal experiments, the drug has been withdrawn from the market, at the request of the Food and Drug Administration. The general question of what is to be done about other drugs and food additives for which species differences in carcinogenicity exist, and for which dose dependency is established is one which will pose difficulties in the future.

BONE DENSITY AND FLUORIDE INGESTION

A high incidence of osteoporosis has been observed in a community with a very low fluoride level in the water supply. The hypothesis is formulated that an optimal level of fluoride may be necessary for the maintenance of normal bone throughout adult life.

During surveys in 1943 and in 1953 in Bartlett and Cameron, Texas, where the water supplies contained 8 p.p.m. and 0.4 p.p.m of fluoride, respectively, N. C. Leone *et al.* (*Fluoridation as a Public Health Measure*, J. H. Shaw, Ed., American Association for the Advancement of Science, Washington, D. C., *p. 110 (1954)*) observed a slightly increased bone density in 16 of the 116 inhabitants of Bartlett and in four of the 121 subjects in Cameron. In a later publication, Leone, C. A. Stevenson, T. F. Hilbish, and M. C. Sosman (*Am. J. Roent. Rad. Ther. & Nuc. Med.* **74,** *874 (1955)*) described these bone conditions in greater detail. In the high-fluoride area of Bartlett, they observed no deleterious bone changes, no unusual incidence of bone fractures, arthritis, hypertrophic bone changes or exostoses, nor any interference with fracture healing. When an increased bone density was observed, the increase was slight and difficult to recognize and bore no resemblance to the bizarre findings described in some cases of long exposure to cryolite or rock phosphate dust. The authors postulated, "There is some indication that the ingestion of excessive fluoride in water and the 'fluoride effect' of the degree encountered in this study may, on occasion, have a beneficial effect in adult bone, as in counteracting the osteoporotic changes of the aged."

A review of the findings of approximately 170,000 roentgenologic examinations of the spine and pelvis of patients primarily from Texas and Oklahoma was conducted by Stevenson and A. R. Watson (*Arch. Indust. Health* **21,** *340 (1960)*). Over 270 communities in Texas and more than 50 towns in Oklahoma have water supplies that naturally contain 0.7 p.p.m. or more fluoride. Twenty-three patients were noted with increased bone density, all of whom had lived from birth in an area where the

water contained from 4 to 8 p.p.m. fluoride. These patients had nothing in common except the roentgenographic observations of their osseous system. All patients were given complete clinical examinations, including serological tests, determinations of the erythrocytic sedimentation rate, enumerations of the erythrocytes, leukocytes and their various forms, measurements of hemoglobin and urea in the blood, and routine procedures of urinalysis. Since many of the patients were in advanced age, they were given electrocardiograms. The physicians who examined the patients were unable to establish any relationship between the roentgenologic findings and the patients' current disease processes or symptoms. Clinical examinations showed no unusual incidence of anemia, arteriosclerosis, arthritis, stiffness of the back, renal disease or biliary calculi.

Another roentgenologic study of 546 persons between the ages of 30 and 70 was conducted in Framingham, Massachusetts, where the water supply contains less than 0.1 p.p.m. of fluoride (Leone, *Arch. Indust. Health* **21,** *324 (1960)* and Leone *et al., Ibid.* **21,** *326 (1960)*). A very precise radiological protocol was followed in order to obtain comparable formation from the various films which were each received and evaluated separately by the radiologists in the study. Among the 546 persons investigated, 279 cases of osteoporosis were found, of which 77 were severe and advanced. Osteoporosis occurred in both males and females and among some individuals who were younger than is ordinarily expected for the appearance of osteoporosis. In addition, the authors observed 14 cases of coarsened trabeculation, 100 cases with calcified abdominal nodes, 118 with calcified vessels, severe bone spurs and ligamentous calcification in 36 persons, and seven cases of Paget's disease of bone. The incidence of these findings was percentagewise higher than for the individuals in either Bartlett or Cameron, Texas. Calcified intervertebral discs, narrowed intervertebral spaces, and collapsed vertebrae were also found in a large number of cases. The authors stated that these data support "the hypothesis that disadvantageous effects on the bone structure of the adult population may be associated with the prolonged use of drinking water that contains an insufficient concentration of fluoride."

The full importance of these surveys is not known at the present time. The high incidence of osteoporosis, particularly of the advanced stages, and among younger age groups in the fluoride-low area of Framingham is indeed disturbing. Comparisons of incidence of bone fractures among middle and older age groups in fluoride and low-fluoride areas are not known to have been made. For the age groups represented by 1,450 high school boys and 1,800 young adults of the Armed Forces, bone fracture experience did not differ over widely varied levels of fluoride in the drinking water (F. M. McClure, *Dental Caries and Fluorine*, American Association for the Advancement of Science, Washington, D. C., *p. 74 (1946)*). However, this age group is not prone to osteoporosis and therefore is not necessarily indicative of the incidence of fractures in older age groups of subjects from communities with different levels of fluorides. Comparable studies are needed for older age groups, especially with regard to fractures of the hip, pelvis, and vertebral column. The suggested correlation of osteoporosis with inadequate fluoride intake in the above studies is sufficiently great that studies to elaborate upon this possible relationship should be organized as soon as possible. It may be that optimal fluoride ingestion in time may prove to be helpful, not only in the presently well-established partial control of dental caries, but also in the partial and highly beneficial prevention of osteoporosis with all the problems associated therewith among our older citizens.

CLEARANCE OF VITAMIN B_{12} FROM PLASMA

Abnormal plasma disappearance curves of vitamin B_{12} are observed in chronic myelocytic leukemia, pernicious anemia in relapse and in remission, total gastrectomy, and malabsorption syndrome.

Vitamine B_{12} is absorbed from the gastrointestinal tract of man through the mediation of "intrinsic factor" (*Nutrition Reviews* **16,** *307 (1958)*). In the plasma, the vitamin is bound predominantly to the alpha globulins, but a small portion may be loosely bound to the beta globulins (W. R. Pitney *et al., J. Biol. Chem.* **207,** *143 (1954)*). From the plasma, vitamin B_{12} is transferred to the tissues (liver) where it is either utilized or stored. The precise mechanisms responsible for transfer of B_{12} across the intestinal wall into the plasma is unknown except that "intrinsic factor" is required for absorption from the gut. The fate of intrinsic factor after it has effected this transfer is obscure. Moreover, the mechanism responsible for transfer of B_{12} from the plasma to the tissues remains to be elucidated.

D. L. Mollin *et al.* (*Blood* **11,** *31 (1956)*) have demonstrated that plasma clearance of radioactive B_{12} is impaired in patients experiencing relapses of pernicious anemia and that the rate of clearance is further diminished in patients with chronic myelocytic leukemia. These findings are considered to be due to the degrees of unsaturation of particular elements in the plasma for vitamin B_{12}. Similar results have been reported by A. Miller *et al.* (*J. Clin. Invest.* **36,** *18 (1957)*) in chronic myelocytic leukemia. These workers suggested that a biochemical abnormality of the plasma is responsible for an increased binding of B_{12} by the plasma proteins, and H. C. Heinrich and S. Erdmann-Oehlecker (*Clin. Chem. Acta.* **1,** *311 (1956)*) have, indeed, demonstrated electrophoretically the presence of increased B_{12}-binding proteins in the plasma of patients with chronic myelocytic leukemia. It has been suggested by I. B. Weinstein *et al.* (*J. Clin. Invest.* **38,** *1904 (1959)*) that the increased binding capacity of plasma from patients with leukemia is associated with an increase in normal seromucoid.

To elucidate further the clearance of vitamin B_{12} from the plasma and to study some of the factors and diseases which modify transfer to the tissues, E. A. Brody, S. Estren, and L. R. Wasserman (*Blood* **15,** *646 (1960)*) have observed the kinetics of intravenously injected radioactive vitamin B_{12} in normal subjects and patients with chronic myelocytic leukemia and pernicious anemia.

One-half microgram of vitamin B_{12} labeled with Co^{58} or Co^{60} was made up into a volume of 1 to 2 ml. and injected into an antecubital vein over a period of 20 seconds or less. Ten to 20 ml. blood samples were withdrawn from the opposite arm frequently for the first two hours (eight to 14 samples) and then at four, eight, 24 hours and daily or every other day thereafter over a two week period when possible. Aside from measurement of radioactivity, microbiologic assay of the "free" and total vitamin B_{12} was carried out with *Euglena gracilis*. Urine passed was collected at 0–1, 0–2, and 2–24 hour periods.

The subjects were divided into four groups: normals, chronic myelocytic leukemics, pernicious anemics in relapse and patients with malabsorption syndrome, and pernicious anemics in remission.

The disappearance curves for all patients studied displayed an initial rapid loss of plasma radioactivity (first 30 minutes) followed by a progressively slower loss of radioactivity in the next 30–90 minutes and finally, a slower exponential clearance of radioactivity.

In normal patients the total serum B_{12} concentrations ranged from 230 to 1,020

$\mu\mu$g. per milliliter. The rate of disappearance of radioactivity from the plasma was approximately the same in all ten patients. The average half-time of disappearance of radioactivity in the initial rapid component was less than three minutes and the final component had a $T_{1/2}$ of approximately 24 hours.

Two leukemic patients were studied; one of these was tested twice within a 15 month interval. The total concentration of vitamin B_{12} was 4,400 and 1,950 $\mu\mu$g. per milliliter in the patient tested twice and 4,100 $\mu\mu$g. per milliliter in the other. It was noted that in both cases the intersection of the initial rapid component ($T_{1/2}$ = 10 minutes) and the slower falling horizontal component occurred at a higher level of radioactivity than in the normal.

Increased capacity of serum from leukemic individuals to bind vitamin B_{12} was studied in these experiments by prior incubation for one hour at 37° C of 0.5 μg. of labeled vitamin B_{12} with 20 ml. of plasma. The mixture was injected intravenously into a "normal" recipient. The result, an intermediate reading between normal and leukemic plasma vitamin B_{12}, may be explained by the increased capacity of leukemic serum to bind vitamin B_{12} *in vitro* as well as *in vivo*.

The total serum B_{12} in cases of pernicious anemia ranged from 12 to 67 $\mu\mu$g. per milliliter. Each such patient demonstrated a plasma clearance which was intermediate between normal and chronic myelocytic leukemia. Clearance patterns were variable, but generally retarded in cases of malabsorption syndrome.

Patients receiving treatment for pernicious anemias usually displayed what appeared to be only partial improvement in B_{12} clearance. Moreover, a patient who had undergone a total gastrectomy four years prior to the development of a typical pernicious anemia, and who had received 50 μg. of vitamin B_{12} three times daily by mouth for one year prior to the intravenous test, displayed a disappearance curve which fell within the lower range of the untreated pernicious anemia group.

There was no significant difference in the percentage of injected radioactivity which appeared in the 24 hour urine samples. *In vivo* probe counting indicated that the injected vitamin B_{12} was taken up almost exclusively by the liver.

Determinations of "free" and total serum B_{12} showed that the bulk of the injected vitamin B_{12} was bound to the serum proteins within three minutes. In normals and in patients with pernicious anemia the total serum B_{12} fell rapidly toward pre-test levels whereas in cases of chronic myelocytic leukemia there was no apparent drop.

When the plasmas of five patients with normal B_{12} levels were saturated by intramuscular injections of 1,000 μg. of B_{12} immediately prior to intravenous injection of labeled B_{12}, the rate of disappearance of radioactivity from the plasma was greater. Vitamin B_{12} incubated with human albumin was not bound to this component of the plasma proteins.

In discussing these results, the authors suggested that the shift of the disappearance curves toward normal in the treated pernicious anemia patients but not within the normal range may be due (a) to the lack of some hypothetical acceptor substance in the liver or (b) the lack of a substance in the plasma permitting the transfer of circulating B_{12} from the blood to the tissues. Perhaps treatment of a patient with pernicious anemia in relapse would not restore this "B_{12}-transferase." The authors further speculate that "B_{12}-transferase" may actually be absorbed "intrinsic factor." This would explain the lack of "B_{12}-transferase" in the blood of patients with pernicious anemia and total gastrectomy. In chronic myelocytic leukemia, the slow clearance of plasma radioactivity may be explained totally by the increased binding capacities of the plasma proteins for vitamin B_{12}.

THE DRUG-MANAGEMENT-OF-OBESITY CONTROVERSY

Amphetamines are considered by one author as mere adjuvants to diet and psychotherapy in controlling hyperphagia; another author considers them highly effective tools in patient management, particularly of obese diabetic patients.

The commercial success of recently introduced complete foods for weight control has been heartening and at the same time an enigma to physicians who cope daily with human obesity. The publicity associated with this latest type of aid in the management of overweight individuals has tended to obscure for the moment a far older approach to the problem, that of drug management.

Despite being hallowed with age, relatively speaking, drug management is by no means uncontroversial as a desirable ally in producing a negative calorie balance. This is well illustrated by a group of four communications published recently. The first is a Council Report on present status and prospect (W. Modell, *J. Am. Med. Assn.* **173,** *1131 (1960)*); the second, an Editorial drawing attention to and commenting on the Report (Editorial, *Ibid.* **173,** *1141 (1960)*); the third, a Letter to the Editor countering the theme of the Report by reference to contrary experiences (Correspondence, *Ibid.* **174,** *199 (1960)*); and the last, an original contribution suggesting advantages of drug management of obesity in diabetes (S. K. Fineberg, *Ibid.* **175,** *680 (1961)*).

In his report to the Council on Drugs of the American Medical Association, Modell summarizes present information on seven different categories of agents used in the control of hyperphagia, the one aspect of the obesity syndrome for which he believes it practical to consider pharmacotherapy. These agents are: (1) central appetite depressants (*e.g.*, digitalis, in overdosage); (2) central-stimulating appetite distracters (amphetamines, amine oxidase inhibitors and other so-called psychic energizers); (3) metabolic stimulants (dinitrophenol, thyroid preparations); (4) sedatives and tranquilizers (amobarbital, chlorpromazine, rauwolfia, meprobamate); (5) bulk producers (methyl cellulose); (6) purgatives and diuretics; and (7) miscellaneous devices (vitamin and mineral preparations, sweets).

The author pays scant attention to category one and to categories three through seven other than to point out that the method is unconscionable (category one); toxic or ineffective (category three); of usefulness restricted to highly specialized circumstances (category four); without effect (category five); of no lasting significance (category six); and without scientific basis (category seven).

In category two, the central-stimulating appetite distracters, the author mentions nonamphetamine-like central stimulants (amine oxidase inhibitors and so-called psychic energizers such as pipradol and methylphenidate) only to point out that these deserve further investigation and trial. His major concern is a review of the amphetamines.

The author does not regard, technically speaking, the amphetamines as true central appetite depressants. Their success is dependent on the patient's drug-induced sense of well-being or "lift," distracting his abnormal drive for food. Central stimulation, therefore, not central depressant effect on appetite, is the common mechanism through which these drugs act. This explains why anorexigenic action has thus far been inseparable from undesirable central stimulant effects (anxiety, increased mental and physical activity, depression, irritability, exhaustion, headache, dizziness, insomnia, increased blood pressure, increased cardiac work and heart rate, cardiac arrythmias, halitosis, dryness of the mouth, burning of the throat, heartburn, nausea, vomiting, diarrhea, tolerance, and habituation) which have constituted their chief

clinical limitations. The loss of olfactory and gustatory acuity, the increased physical activity, and a depressant effect on gastrointestinal activity, even when combined, are of slight consequence. Taken together, all effects of the amphetamines do not produce sufficient appetite depression to make obese patients lose weight without simultaneous dietary caloric restriction. Hence, many authorities have regarded these drugs as mere accessories which should be eliminated from the total regimen for weight reduction at as early a date as possible.

Modell provides a long list of compounds, accompanied by their trade names, all of which belong to the family of amphetamines. Although manufacturers of the newer amphetamine congeners have avoided mention of, and even disclaimed links between, their compounds and amphetamine, Modell demonstrates simply, in a figure containing structural formulas of seven compounds, that all contain a common chemical configuration which apparently confers the cephalotropic action. Hence, it becomes almost a certainty that the so-called anorectic effect is the direct consequence of the central stimulant action common to all. Tolerance and habituation have developed during clinical experiences with the older, and with one of the newer, members of the amphetamine group. Since the fundamental action of all seems the same, tolerance and habituation will probably develop with all and, therefore, none is desirable for prolonged therapy.

Modell discusses in detail the problems posed by the evaluation of the effectiveness of amphetamine compounds. Patients participating in double-blind control investigations frequently distinguish between placebo and the drug being tested, usually by the easily recognizable central stimulating effects of the latter. This reduces the sensitivity of the method of clinical evaluation of these drugs and also makes difficult the design of studies in which these factors do not bias results. When doses are so small as to avoid central stimulating effects, they also are likely to be too small to influence overeating and hence produce negative results or results due solely to placebo action. Usually, therefore, reports of drug-induced weight loss without disturbing psychic effects are of doubtful validity. In any member of the amphetamine series, consequently, there is no evidence that the central stimulant actions are so segregated that the drug affects overeating while losing its tendency to cause restlessness, insomnia, and anxiety.

Modell concludes his report by stressing the futility of looking to new variants of old drugs to provide the solution to the hyperphagia problem. He regards drugs solely as adjuvants to carefully controlled diet and psychotherapy. In these conclusions he receives support editorially (*J. Am. Med. Assn.* **173,** *1141 (1960)*) when it is pointed out that over 90 per cent of obesity cases are not related to defects which in any way disturb the physiological appetite mechanism. The editorial implies that any approach to obesity based on physiological considerations rather than psychological ones is doomed to failure and very apt to aggravate the psychic disturbance underlying the hyperphagia.

This view on obesity in general and on nonpsychiatric control of hyperphagia is contested in a Letter to the Editor (*J. Am. Med. Assn.* **174,** *199 (1960)*) which refers to 30 years of experience to the contrary. The correspondent points out that certain individuals, while obese, are not hyperphagic but rather hypophagic. Some patients, it is claimed, do have obesity based on an interference with fat metabolism in water-logged tissues, while others have difficulty in mobilizing fat for metabolic utilization. The writer, in other words, cries out against therapeutic nihilism in regard to obesity.

Modell's views on drugs for obesity are challenged also in a report on the use of anorexigenic drugs in the treatment of obesity-diabetes (*J. Am. Med. Assn.* **175,** *681 (1961)*). Fineberg points out the necessity of attacking the obesity as the prime target

in this disease and presents data to support the thesis that weight reduction with the aid of anorexigenic agents is superior to either insulin or oral hypoglycemic agents in the management of obesity diabetes.

In his original investigation (*Ann. Int. Med.* **52,** *750 (1960)*), Fineberg set out to find out if an anorexigenic agent, presumably sufficiently free from sympathomimetic effects for use in diabetics with hypertension and hypertensive cardiovascular disease would produce weight reduction in patients all of whom were obese and not losing weight despite weight-reducing diets prescribed long before. Sixty-two obese diabetics were given either a placebo or phenmetrazine hydrochloride, a highly publicized typical amphetamine congener which Modell describes as of about the same effectiveness as dextroamphetamine with relatively little effect on the cardiovascular system, in doses of 25 mg. three times daily in the typical double-blind procedure. In an attempt to answer Modell's criticism of the double-blind technique in studying the amphetamine drugs, Fineberg concealed from the patients the type, mode of action and possible side effects of the drug and made no mention of diets, dieting or appetite. Although 72 per cent of the group given phenmetrazine hydrochloride lost weight as opposed to only 12 per cent of the placebo group, 13.5 per cent of the 37 patients who received the drug had to discontinue it because of untoward central nervous system stimulation.

The results of this investigation, together with claims of the development of new amphetamine drugs with pharmacologic activity but less central nervous stimulation, led to the design of another study in which diethylpropion was selected for a controlled comparative evaluation with phenmetrazine. Forty-two patients, selected for obvious gross obesity and failure to lose weight on prescription of 1,000 to 1,500 calorie diabetic diets, participated in the investigation. On reporting for clinic visits, patients received coded capsules alternately containing 25 mg. of phenmetrazine hydrochloride or 25 mg. of diethylpropion. As in the previous study, the author introduced what he calls a "third-blind" in that the patients were not informed of the purpose or the supposed action of the medications. Patients were instructed to take one capsule 30 to 40 minutes before breakfast and one hour before the other two meals, *i.e.*, three times daily. No additional dietary instructions were given and no changes in insulin or other medications were introduced. After a six week course on one drug, each patient then received without his knowledge of a change in medication, a six week course of the other drug.

Of the 21 patients who began with phenmetrazine hydrochloride (Group A), four were dropped for poor co-operation and three had to discontinue taking the drug because of side effects. Two of the latter could not tolerate diethylpropion. The final number completing both courses in Group A was 14. The incidence of significant side effects in all 33 patients given phenmetrazine hydrochloride was 9.1 per cent.

Of the 21 patients who began with diethylpropion (Group B), four were dropped for poor co-operation and one had to discontinue the drug because of side effects. The final number completing both courses of Group B was 16. The incidence of significant side effects in all 31 patients given diethylpropion was 3.2 per cent.

In the first six weeks, the 14 patients in Group A lost an average of 3.0 kg., with only one patient failing to lose. Weight losses in the remaining 13 ranged from 1.5 to 8.2 kg. In the first six weeks, the 16 patients in Group B lost an average of 1.3 kg. with three failing to lose at all and seven failing to lose a significant amount. Weight loss in the remaining six ranged from 1.6 to 5.0 kg.

In the second six weeks, the 14 patients in Group A lost an average of 0.6 kg., with half actually gaining weight. Weight loss in the remaining seven ranged from 0.3 to 4.3

kg., with the weight loss in only one exceeding the prior loss on phenmetrazine hydrochloride. In the second six weeks, the 16 patients in Group B lost an average of 1.6 kg., with all patients participating in weight losses ranging from 0.1 to 3.0 kg. The weight loss in ten equalled or exceeded the prior loss on diethylpropion.

The average age of these 30 patients (Groups A and B combined) was 55 years (range 25 to 74 years). Twenty-three were female, seven male. The average known duration of their disease was 7.5 years. Sixteen were on insulin and seven were taking oral hypoglycemic agents at the onset of the investigation. Twelve of those taking insulin noted a drop in insulin requirement and six discontinued insulin entirely. Four taking oral hypoglycemic agents reduced their dosage and two discontinued the therapy.

Fineberg concludes that phenmetrazine hydrochloride has stronger anorexigenic qualities than diethylpropion and appears to be an agent which will cause an involuntary reduction of caloric intake. In addition, phenmetrazine hydrochloride, unlike diethylpropion, was able to produce some anorectic effect when given after a previous course of the other drug. Symptoms of central nervous system stimulation were more numerous with phenmetrazine hydrochloride than with diethylpropion. The results of this investigation support the concept expressed by Modell that the anorexigenic potency and central nervous system stimulation can not be separated without impairing the former.

Fineberg, however, objects to Modell's hypothesis that these drugs act only as "central-stimulating appetite distracters." He feels it does not explain clinically apparent appetite suppression observed often in the absence of clinically observable central sympathomimetic stimulation or psychic uplift. He also cites indications in the cat that direct stimulation of a satiety center in the ventromedial nuclei of the hypothalamus results in diminished food intake by inhibition of the appetite center in the lateral nuclei (B. K. Anand and S. Dua, *Indian J. Med. Res.* **43,** *113 (1955)*) and the suggestion that amphetamine derivatives probably produce appetite suppression by excitation of this portion of the hypothalamus (J. R. Brobeck, S. Larsson, and E. Reyes, *J. Physiol.* **132,** *358 (1956)*). He points also to the work of others (F. R. Stowe, Jr. and A. R. Miller, Jr., *Experientia* **13,** *114 (1957)*; and J. Tepperman, *Perspect. Biol. Med.* **1,** *293 (1958)*) suggesting the probable locus of action of the amphetamines to be at the lateral nuclei or feeding center and that the action is a direct suppression of that area. He admits, as pointed out by Modell, (*v.s.*), that the mechanism of action of amphetamines remains a mystery.

Fineberg suggests in his summary that obese diabetic patients carefully selected for mildness of disease, insulin dependence, and maturity of age (as opposed to the random selection used in his series) could replace insulin more successfully with diet and anorexigenic drugs than with oral hypoglycemic agents. Deploring the use of oral hypoglycemic agents as a "therapy-of-convenience," he asks that present day enthusiasm for these agents be transferred to effective appetite-suppressing agents.

These discussions of the role of drugs in weight control emphasize the breadth of opinion current in theory and practice. Despite conscious efforts to minimize its effects in clinical investigations, the *modus operandi* or personality of the individual physician undoubtedly acts in some measure to produce success or failure in controlled investigations and is unquestionably a major factor in determining the results arising from purely clinical situations. It is unfortunate when physicians of medicinal persuasion in regard to therapy fail to recognize their own participation in the methodology of the psychiatrist. The short-term aim of the practitioner must remain the amelioration of his patient's health regardless of the techniques used. The rational therapy of obesity, as noted editorially (*J. Am. Med. Assn.* **173,**

1141 (1960)), requires, as do rational therapies for all medical syndromes, an understanding of, as well as an attack against, the causes of the disturbance. Hence, in the syndrome of obesity, completely rational therapy must await further understanding of the processes involved in the causation of hyperphagia.

EXERCISE AND BLOOD AMMONIA LEVELS IN MAN

Mild or moderate muscular activity causes greater increases in the ammonia level of the blood in cirrhotic patients than in patients with liver disease or in normal individuals.

Patients with decreased functional capacity of the liver, as those with cirrhosis, develop ammonia intoxication when given diets with even modest protein intakes. In such states the blood ammonia level may rise and the patient develops characteristic signs and symptoms along with electroencephalographic changes. The cause of the increased ammonia level may be the decreased capacity of the liver to convert ammonia to urea or to anastomoses in the portal system which permit much of the portal venous blood to bypass the liver and add its ammonia content to the general circulation.

S. P. Bessman and J. E. Bradley (*New Engl. J. Med.* **253,** *1143 (1955)*) reported that the peripheral tissues extract large amounts of ammonia from the blood. The possibility exists that the extraction of ammonia by peripheral tissues may in some way protect more sensitive areas of the body from the high ammonia levels.

Recently, S. I. Allen and H. O. Conn undertook a series of investigations to determine the effect of muscular exercise on the release of ammonia from peripheral tissues in both normal and cirrhotic individuals (*Yale J. Biol. Med.* **33,** *133 (1960)*). For their study they had three groups of individuals: ten normal male volunteers, 31 male ambulatory patients who had various benign nonhepatic disorders, and 17 male patients who had histologically proven cirrhosis of the liver. These investigators determined the blood ammonia levels in the individuals before and after a series of graded exercises involving only one hand. The exercises required that all subjects were in the supine position and had been resting for at least 15 minutes. None was allowed any vigorous muscular exertion before the blood was collected nor were they allowed to clench or squeeze their fists prior to or during the blood collection. For mild exercise the individuals clenched their fists vigorously 100 times at the rate of one per second. For a more strenuous exercise the subjects gripped a double spring hand grip exerciser ("Power gripper") for 50 times at the rate of one per second. One hundred such power grips at the same rate were sufficient to fatigue the forearm muscles of all normal subjects. This was defined as severe exercise.

In ten control patients the blood ammonia level before exercising was 127 ± 21 μg. per 100 ml. in the venous blood. No change was noted after mild exercise (clenching the fists). On the other hand the cirrhotic patient who had a little higher resting blood ammonia level, 151 ± 26 μg. per 100 ml., showed an increase of 43 ± 22 μg. per 100 ml. after exercising. The difference between the control and cirrhotic patients after exercise was statistically significant, $P < 0.01$.

After moderate exercise the six control patients had an increase in the blood ammonia which was not considered significantly different from the resting values (5 ± 24 μg. per 100 ml.). On the other hand the increase in the venous blood ammonia for the seven cirrhotic patients after exercise was 80 ± 35 μg. per 100 ml. ($P < 0.001$).

In studies involving severe exercise, normal nonhospitalized subjects had an average increase in the blood ammonia of $90 \pm$

69 μg. per 100 ml. with a resting value of 161 μg. per 100 ml. The ten control subjects had an increase of 128 ± 87 μg. per 100 ml. following this type of exercise while the level for the cirrhotic patients increased 122 ± 49 μg. per 100 ml. The difference between these three groups was not statistically significant.

In this study it appears that the ammonia metabolism in the cirrhotic patient releases larger amounts of ammonia from the muscles during mild and moderate exercise than do the control patients. However, after fatiguing exercise, both groups of patients added large amounts of ammonia to the venous blood. The elevations in the blood ammonia level were not dependent upon the liver condition after severe exercise.

In addition to measuring the ammonia level in the blood obtained from the exercising arm the investigators took samples from the resting arm. While the ammonia level rose from 190 to 300 μg. per 100 ml. in the cirrhotic individuals in the blood obtained from the exercising arm, the level in blood obtained from the resting arm did not change significantly. This was true for the normal individuals, the control subjects, and the cirrhotic individuals. Thus, one gets a liberation of ammonia from muscles which are exercising, but finds there is no increase in the blood ammonia obtained from either the arterial or venous blood draining the resting arm.

In cirrhotic patients with impending hepatic coma, the diuretic acetazoleamide has been reported to induce coma and also decrease the arterial venous ammonia difference. This drug was given orally 13 hours and one hour prior to studying the effect of muscular activity on blood ammonia levels in a group of cirrhotic patients. It was found that the average blood ammonia difference before and after strenuous exercise was 124 ± 40 μg. per 100 ml. and the difference in the same group before and after receiving acetazoleamide was 115 ± 55 μg. per 100 ml. Thus the administration of this diuretic apparently did not influence the release of the ammonia from the muscle following exercises. While the mechanism by which the ammonia is released after muscular exercise is not fully understood, this study also demonstrates how exercise or even clenching fists before drawing blood may give erroneous blood ammonia levels. It also suggests the importance of bed rest (lack of muscular activity) in patients who have severe hepatic cirrhosis.

CLEARANCE OF INTRAVENOUS FAT

Artificial oil emulsion was injected intravenously in patients and its rate of disappearance from the blood of a control group was compared with that of an infarction group and a group with peripheral vascular disease.

The turbidity of plasma following a fatty meal results from an increased concentration of chylomicra. Studies summarized in the following reports—A. Waldow, J. E. Chapman, and J. M. Evans (*Am. Heart J.* **47,** *568 (1954)*), D. W. Barritt (*Brit. Med. J.* **2,** *640 (1956)*), and J. R. A. Mitchell and B. Bronte-Stewart (*Lancet* **1,** *167 (1959)*) have indicated that patients who had cardiac infarction showed a greater intensity and duration of lipemia following the ingestion of fat.

Triolein labeled with I^{131} has been fed in studying the difference in lipemia between controls and patients with cardiac infarction. One of the problems in interpreting studies of this sort arises because of the concomitant processes of intestinal absorption and clearing of fat. For this reason the authors of the present study, M. L. Mashford and P. J. Nestel (*Circulation Research* **9,** *7 (1961)*), chose to eliminate the effect of absorption by administering the fat intravenously.

Although the authors felt that ideally the fat should be in the form of a standard chyle, its preparation was considered to be too difficult. Thus a commercially available oil emulsion was utilized. Five groups of patients were studied. Group I consisted of 12 subjects either healthy or recovering from illnesses not related to the cardiovascular system. Group II was made up of ten patients who had had a myocardial infarct five to six months previously and were not receiving medication. Group III patients had myocardial infarcts five to 12 months previously and had received heparin twice weekly during the three months prior to the test. Group IV patients were treated with phenoprocoumon anticoagulant therapy continuously from the time of infarction three to nine months before the experiment. Group V was composed of eight patients with intermittent claudication. Of these four had angina pectoris and two had a history of myocardial infarction.

Each subject was given an infusion of 80 ml. of fat emulsion over a 30 minute period after an overnight fast. Blood samples were collected in oxalate before the infusion and at ten minute intervals for one hour after the start of the infusion and at 20 minute intervals for a second hour. Plasma was separated and optical density (O.D.) was read in a spectrophotometer at 650 mμ.

Lipemia developed in all subjects so that curves showing the relationship of optical density to time could be made and examined. The usual shape of the curves included a linear rise until the end of the infusion at 30 minutes followed by a fall. The peak O.D.'s were not all reached at the same time, however. In all but the controls delayed or sustained peaks were evident. The phenoprocoumon group showed the most frequent increase in O.D. after the end of the infusion. Comparison of the curves was facilitated by plotting mean curves for each group on a single graph.

Calculation of the peak O.D. minus initial O.D. per unit of time gave the rate of rise of O.D. The time for the O.D. fall to reach 50 per cent of the peak level was used as the index of rate of decrease.

Study of the mean curves showed that the peripheral vascular disease curve resembled the curves for controls and untreated infarct groups. Striking differences were apparent between the curves of the heparin-treated and phenoprocoumon-treated groups and those from the untreated infarct groups, however. The peak O.D. average was higher in the phenoprocoumon-treated group and lower in the heparin-treated subjects.

The O.D. rose more slowly in the heparin-treated group and more rapidly in the phenoprocoumon-treated group. Although the graphs of mean optical densities showed differences in the rates of rise, the mean difference between the untreated infarct group and the phenoprocoumon-treated group was not significant. The mean differences in rate of rise between the treated infarct groups and the controls were not very significant, possibly due to the great variability in the controls.

Although the differences were not significant, the time for O.D. to fall to 50 per cent was longer in the untreated infarct group than in the heparin-treated group and still longer in the phenoprocoumon-treated group.

These results indicate a normal clearing of injected fat emulsion in the untreated infarct group and in the peripheral vascular disease group in contrast to the findings when fat was given orally. Since the normal fat absorption is about 95 per cent, it is not likely that increased absorption could explain the difference in lipemia. Another possibility is that the state of emulsification is abnormal.

The clearing of artificial emulsion particles appears to proceed in the same way in both normal and infarct patients whereas the latter seem to be unable to remove from the blood the chylomicra derived from a fatty meal. Evidence that chylomicra from infarct patients may differ from the normal

has been reported by D. F. Davies (*Clin. Sci.* **18,** *263 (1959)*) who observed that these particles manifest a decreased electrophoretic mobility.

The earlier finding that chylomicra of infarct patients eating a fatty meal are not cleared as readily as the normal does not necessarily conflict with the finding that injected oil emulsion can be cleared in these patients but, according to the authors, helps "focus attention on the chylomicra themselves as a likely site for these differences."

REDUCTION OF SERUM CHOLESTEROL BY TETRAIODOTHYROFORMIC ACID

Tetraiodothyroformic acid lowered the serum cholesterol by 75 mg. per 100 ml. in 16 of 20 hypothyroid patients and in two of six euthyroid patients; all had severe coronary artery sclerosis.

In the extensive search for agents which will lower the level of cholesterol in the blood and so might help prevent atherosclerosis, thyroid gland and thyroxine have been passed over. True, they are active, but the hypermetabolism induced by the doses necessary in euthyroid subjects has made these agents impractical. One alternative has been to study the effects of D-thyroxine, the nonphysiologic isomer (P. Starr, P. Roen, J. L. Freibrun, and L. A. Schleissner, *Arch. Int. Med.* **105,** *830 (1960)*), and of various synthetic thyroxine analogues which might have little calorigenic effect but potent hypocholesterolemic action (*Nutrition Reviews* **18,** *249 (1960)*).

E. Corday, H. Jaffe, and D. W. Irving have turned their attention particularly to tetraiodothyroformic acid (*Arch. Int. Med.* **106,** *809 (1960)*). The authors point out that since 1927 this and other analogues of thyroxine have been known to have little calorigenic effect and, more recently, have been shown to have a strong cholesterol-lowering effect in the rat.

Corday's group gave tetraiodothyroformic acid (T_4F) to 26 patients with severe coronary atherosclerosis and hypercholesterolemia. Six were euthyroid and 20 had hypothyroidism induced by radioactive iodine for the relief of intolerable angina pectoris. The hypothyroid patients generally could not take more than $\frac{1}{10}$ grain of thyroid (6 mg.); a few could take 1 grain per day.

Three control blood cholesterol levels were determined over a period of weeks. A placebo was then given for two to 12 weeks and the blood cholesterol again measured at intervals of two weeks. Then 100 mg. of T_4F was given per day and cholesterol levels were measured every two weeks. The authors increased the dose every other week in the first 12 patients up to 600 mg. per day in order to learn how much could be given without calorigenic effects. Nine patients could not take more than 400 mg. per day because of nervousness, palpitation or angina.

The blood cholesterol level fell 75 mg. per 100 ml. or more in 18 of the 26 patients. The drug was then withheld; hypercholesterolemia returned within four weeks. After this, smaller doses of 25 to 100 mg. were given and the patients were followed for nine or more months.

Tetraiodothyroformic acid lowered the blood cholesterol in 16 of the 20 hypothyroid patients and in two of the six who were euthyroid. The average control value was 372 mg. per 100 ml. and the "average post-therapy reduction in blood cholesterol was 142 mg. per 100 ml (38%)." (Here there is a discrepancy with the tabulated data which indicate a somewhat lesser fall.) More than 200 mg. of T_4F caused angina in eight cases and nervousness or palpitation in four. The authors found 100 mg. per day safe in all but three patients; two of these could take

50 mg. per day, which was enough to lower their blood cholesterol level.

Two patients, one receiving 300 mg. of T_4F per day, showed rising cholesterol levels after the fifth month. After discontinuation for two weeks the drug was again effective. The blood cholesterol rose in all patients within two to four weeks after the medication was discontinued, exceeding control levels in six patients for as long as eight weeks.

Heart pain occurred within four hours of an excessive dose of tetraiodothyroformic acid and disappeared within a day when the drug was stopped. No toxic effects of T_4F were found on the blood, liver function or on the blood uric acid level. Three patients lost weight. The drug apparently precipitated atrial tachycardia in two patients who had had previous attacks.

The results of basal metabolism tests were "very confusing" but are not detailed. Corday, Jaffe, and Irving conclude that the "favorable cholesterol-lowering effect" of T_4F occurs at about $\frac{1}{6}$ of the dose needed "to induce a disturbing calorigenic effect in the brittle hypothyroid, coronary patient."

From the fact that the cholesterol level fell by one-third in 16 of 20 hypothyroid patients with coronary atherosclerosis, the authors infer that the drug might prevent arteriosclerosis in individuals with hypercholesterolemia. As Corday's group points out, there are autopsy studies of subjects with long-standing hypercholesterolemia and no coronary arteriosclerosis. Nevertheless, they believe that patients with blood cholesterol levels of over 300 mg. per 100 ml. should be treated and they "would advocate the use of thyroid analogues in the treatment of hypercholesterolemia of all patients with cerebral, coronary, renal, and peripheral arteriosclerosis."

However, since four of the six euthyroid patients with hypercholesterolemia showed no effect on their serum cholesterol levels, a more limited conclusion appears safer, namely, that thyroxine and its analogues are most effective in thyroid deficiency. Because a physiologic substance (or analogue) has a striking effect on the deficient patient, one cannot extrapolate and expect the same result in the nondeficient subject. It is well recognized that the hypothyroid patient is very much more responsive to thyroxine in many or all respects than is the normal subject. In particular, the serum cholesterol level responds rapidly and may return to normal even before the basal metabolism and serum precipitable iodine have been appreciably affected. This is in keeping with the idea that the increased serum cholesterol in hypothyroidism does not have the same cause as that occurring "spontaneously" or in other clinical states. The authors do recognize that T_4F may or may not be effective in various other conditions with hypercholesterolemia.

Indeed, K. W. Berge *et al.* (*Proc. Staff Meetings Mayo Clinic* **36,** *171 (1961)*) found that tetraiodothyroformic acid had only slight effect in four out of the five euthyroid hypercholesterolemic patients they studied. It caused severe heart pain in the fifth. The authors concluded that the drug is not useful in the management of patients with hypercholesterolemia.

Another limitation applies to the conclusions drawn from studies which measure cholesterol and ignore other serum lipids. The latter do not necessarily parallel cholesterol levels. For example, serum neutral fat is not increased even in severe hypothyroidism associated with very high serum cholesterol levels. Since one does not know which lipids, if any, are causes of atherosclerosis, it is unwise to attribute preventive value to lowering serum cholesterol. This becomes even more confusing when one studies such diverse groups as euthyroid and hypothyroid subjects together, or conditions with normal serum neutral fats and others (*e. g.* the nephrotic syndrome) with very high levels.

Thus, to conclude that an agent which lowers serum cholesterol will protect against

atherosclerosis and to prescribe it regularly in adult patients seems premature. For even when a completely preventive regimen is developed it will be difficult to do much for adults who have already spent 40 to 60 years acquiring their atherosclerosis.

OBESITY IN CHILDHOOD AND ADULTHOOD

At least 33 per cent of the adults who are obese were overweight as children. From two to five times as many overweight children become obese adults as do normal or underweight children.

A few years ago, A. G. Mullins (*Nutrition Reviews* **17,** *99 (1959)*) made a retrospective study of obese patients in a London outpatient clinic. He found that of 373 consecutive outpatient admissions, 26 per cent of the men and 44 per cent of the women were more than 20 per cent above "standard" weight. The incidence of obesity in this outpatient group was approximately 33 per cent.

Approximately one-third of these patients had been obese from childhood, as evidenced by the fact they had been called "fatty." These patients showed a high incidence of psychological abnormalities as evaluated by clinical examination. The clinical impression also suggested that intelligence and extent of schooling were much less in the group that had been obese from childhood. Attempts to reduce the body weight of these obese subjects were singularly unsuccessful.

Mullins pointed out that "persistent juvenile obesity is an important cause of obesity in adult life and is, therefore, a potentially dangerous condition."

A more objective evaluation of the influence of extra body weight in childhood upon the development of obesity in adulthood was made by S. Abraham and M. Nordsieck (*Pub. Health Reports* **75,** *263 (1960)*). They used the height-weight records secured on children in three elementary schools in Hagerstown, Maryland from 1937 to 1939 as the basis for their study. At that time, careful physical measurements were made on approximately 2,000 boys and girls between the ages of ten and 13 years.

Height was determined without shoes; weight was determined without shoes, sweaters or coats, but with the usual indoor clothing. The actual height and weight of each child was compared with the average of the Baldwin-Wood height-weight tables. The body weight of 12.7 per cent of the boys ranged from 70 to 89 per cent of the Baldwin-Wood averages; 75.2 per cent ranged from 90 to 109 per cent, and 12.1 per cent were above 110 per cent. The body weights of 23.4 per cent of the girls were from 60 to 89 per cent of the Baldwin-Wood averages; 61.0 per cent were from 90 to 109 per cent and 15.6 per cent were 110 per cent or more.

To choose the subjects for the follow-up, the children were arranged in decreasing order according to the degree that their weights exceeded the average of the Baldwin-Wood tables. Fifty children, or about 5 per cent of the heaviest children from each sex, were selected as overweight. One hundred children were also selected for the "average weight" group. The body weights of these children ranged from 95 through 104 per cent of the Baldwin-Wood averages.

The follow-up study was made in the summer of 1958. At that time only 174 (or 87 per cent) of the 200 children in the earlier study could be located. Fifty-four were eliminated because they had moved from the area. This left a total of 120 on which the follow-up was based.

The average age of the adults was 31 years, with a range from 26 to 35. For both sexes, the study indicated that overweight children tend to become overweight adults

more often than do children of average weight. Of the overweight boys, 86 per cent were overweight as adults. Of the average weight boys, 42 per cent were overweight as adults. The susceptibility to obesity in adulthood is thus twice as great if the boy is overweight.

Approximately 80 per cent of the overweight girls became overweight women. On the contrary, only 18 per cent of the average weight girls became overweight adults. Of the moderately overweight girls, 50 per cent were average weight or less as adults. This is in contrast to the 8 per cent of the markedly overweight girls who were average weight or less as adults.

Both of these studies emphasize the persistence of childhood obesity into adult years. The work of Mullins stresses the importance of preventing or correcting childhood obesity as this condition is difficult to treat if it extends into adulthood.

EFFECTS OF VITAMIN E AND COD LIVER OIL IN MAGNESIUM-DEFICIENT CALVES

Cod liver oil feeding may reduce the alpha tocopherol in a whole milk diet, but the soft tissue changes including increased calcium content are a reflection of magnesium deficiency. Cod liver oil appeared to have a specific electrocardiographic effect which was not counteracted by adding alpha tocopherol to the diet.

Many reports on experimental magnesium deficiency in calves have suggested that multiple factors may be involved in the pathological changes which occur. Reviewing the clinical and pathological observations K. L. Blaxter, J. A. F. Rook, and A. M. MacDonald (*J. Comp. Path. Therap.* **64,** *157 (1954)*) suggested that the histopathological changes attributed to magnesium deficiency, especially the calcification of the soft tissues, might have been the result of the development of a tocopherol deficiency since cod liver oil was included as a source of vitamins A and D in the magnesium deficient diets.

The suggestion of Blaxter, Rook, and MacDonald was not confirmed by J. W. Thomas and M. Okamoto (*J. Dairy Sci.* **41,** *724 (1958)*) who included extra alpha tocopherol in their whole milk diet yet still obtained calcification of the heart and large blood vessels in calves on the magnesium deficient diet. However, the uncertainty of the effects of a deficiency of magnesium as compared with a deficiency of tocopherol and the effects of additional cod liver oil in the diet led B. A. Dehority *et al.* (*J. Dairy Sci.* **44,** *58 (1961)*) to investigate the effects of the addition of magnesium, alpha tocopherol, and cod liver oil respectively to diets for calves essentially limited to whole milk.

The magnesium deficiency produced by feeding a whole milk diet supplemented with essential minerals (except magnesium), concentrates of vitamins A and D, and chlortetracycline is not as acute or as severe as that produced by feeding diets of a semi-synthetic type simulated milk or by feeding a whole milk diet which had been subjected to ion exchange techniques to remove magnesium. On the other hand, over a 28 week period, magnesium deficiencies do exist and the alterations in these deficiency symptoms by the presence or absence of tocopherol and/or cod liver oil indicate the relationship of these dietary items.

The addition of magnesium as magnesium chloride or the addition of cod liver oil in the absence of alpha tocopherol increased the incidence of diarrhea in these calves, but no balance studies were run on the animals and the effect of these scours upon the changes observed in tissues could not be evaluated. If the scours were accompanied by elevated body temperature, the animals

were treated with sulfamethazine intravenously in an attempt to reduce this variable and to control the possible pathogenic organisms which might be involved.

Calves given 2.5 g. of magnesium as magnesium chloride daily showed significantly higher serum phosphate and serum magnesium values at the end of 28 weeks. In addition, there was a higher level of total alpha tocopherol in the blood.

Of particular interest was the lowered heart and muscle calcium and the increased heart and muscle magnesium which occurred as a result of the magnesium supplementation of these diets. The increased magnesium values of the heart and muscle occurred only if alpha tocopherol had not been given as a supplement in these diets. The changes in bone composition as a result of magnesium supplementation included lowered calcium and increased magnesium.

The addition of cod liver oil to a calf diet produces an alpha tocopherol deficiency. Therefore, it is notable that when cod liver oil was added to the whole milk diet of these calves, the rate gains were reduced. The electrocardiographic changes occurring with the addition of cod liver oil to these diets (longer P-R and Q-T intervals) were not corrected by the addition of alpha tocopherol to the diet, suggesting that these changes may be due to a more specific action of cod liver oil than the reduction of alpha tocopherol.

The addition of cod liver oil to these diets increased the phosphorus and the vitamin A in the serum, lowered the magnesium value and the tocopherol value, lowered carotenoid content of the blood serum, and increased urea level.

The addition of cod liver oil to the diet had a more generalized effect on the tissues: on both a fresh weight and dry weight basis there were reduced phosphorus, magnesium, potassium, creatine, and total nitrogen values. In the wet tissues there was a reduced dry matter, and in all tissues there was a reduction in tocopherol. As might be expected, addition of cod liver oil to the diet increased the calcium and sodium in the soft tissues and the calcium of bone. There was a reduction in magnesium in the bone.

With the exception of the changes observed in the electrocardiographs of these calves, the addition of tocopherol counteracted all of the effects of the cod liver oil, confirming earlier observations that much of the effect of cod liver oil in the diet of calves was due to the production of an alpha tocopherol deficiency.

The studies of Dehority *et al.* have again emphasized the multiple factors which may be involved in the development of symptoms of a mineral element deficiency. However, they do not confirm the suggestions of Blaxter, Rook, and MacDonald that the soft tissue changes due to magnesium deficiency are in fact due to alpha tocopherol deficiency. The data of these and other workers increasingly emphasize the need to consider the total picture in evaluating a dietary deficiency.

EATING HABITS AND ATHEROSCLEROSIS

Chickens were divided into two groups and fed atherogenic diets either for two one-hour periods ("meal eaters") or with free access 24 hours per day ("nibblers"). Both induction and regression of atherosclerosis were studied.

Earlier studies of the influence of diet on the organism have dealt primarily with the effect of alteration of diet composition. Recent studies have shown that the way the diet is eaten may also influence metabolism significantly. If animals eat frequent small feedings rather than spaced full meals they will tend to deposit less body fat, retain

more protein, and have a more active thyroid.

Civilized man has become a meal eater as a result of habit, custom, and working conditions and he also shows a high frequency of atherosclerosis. In view of this correlation, C. Cohn, R. Pick, and L. N. Katz (*Circulation Research* **9**, *139* (*1961*)) became interested in determining whether the pathogenesis of atherosclerosis could be related to the pattern of diet ingestion.

Comparable groups of chickens were fed diets designed to aid the production or regression of atherosclerosis. These rations were fed either as meals or ad libitum. The male chickens used were received when one day old and were fed for eight to ten weeks on chick starter mash before the experiments were begun.

Experiment I was designed to compare the induction of atherosclerosis in two groups of chickens. The diet used included 20 per cent protein, 5 per cent cottonseed oil, and 0.5 per cent cholesterol. Group (a), the "nibblers" (ten birds) had diet available 24 hours per day but group (b), "meal eaters" (ten birds) received food for one hour only in the morning and afternoon. After five weeks of the experiment the animals were bled and sacrificed. Aortas were examined grossly and the atherosclerotic lesions were graded according to severity. The coronary arteries were studied histologically. Serum cholesterol, phospholipid, and esterified fatty acids were determined. Experiment II resembled the first except that it lasted longer and less cholesterol was given.

Experiment III was designed to study the effect of meal eating *versus* nibbling on the regression of atherosclerosis. The atherogenic diet which included 20 per cent protein, 5 per cent cottonseed oil and 1 per cent cholesterol was fed twice daily (meal eating) to 34 chickens (eight weeks old) for five weeks. Ten were sacrificed for histological determination of the extent of "base line" atherosclerosis. A regular mash diet was fed the surviving birds either as discrete meals or ad libitum (nibbling) for the next two weeks. As the regression of lesions in the aorta is very slow, study of regression effects was confined to the coronaries.

Experiment IV resembled III. There were three groups of chickens, 60 eating ad libitum, 95 eating two meals daily and 98 eating three meals daily of the atherogenic diet used in Experiment III. At the end of the five week induction period birds were autopsied from each group to establish the "base line" degree of atherosclerosis. Subsequently all birds were fed the "nonatherogenic" mash diet, the nibblers continuing to eat ad libitum, but the meal eaters being divided into two groups, one of which was continued as meal eaters and the other allowed to revert to nibbling. At the end of the two weeks, half of the birds of each group were autopsied for evaluation of coronary atherosclerosis. The other birds were studied after three weeks.

Meal eating resulted in the consumption of about one-third less food and a smaller weight gain by this group. Serum cholesterol and lipid concentration were increased and the incidence and severity of gross atherosclerosis of the thoracic aorta were greater. In the meal-eating birds, microscopic coronary atherosclerosis was significantly greater both in incidence (twice) and involvement (seven times) than in the nibblers.

Serum cholesterol was rapidly returned to normal in the nibbling chicken after shifting from a cholesterol-containing diet to a regular mash diet. In contrast, meal-eating birds showed a much slower decline in serum cholesterol while on the same diet regimen. Two weeks after eating a regular mash diet the serum cholesterol levels of the meal eaters were approximately double the normal and were still elevated after three weeks.

The plaques of the nibbling birds regressed rapidly during the two and three week periods. The rate of regression was noticeably slower in the meal-eating groups. In

two groups the lesions were so severe that evidence of regression was not seen before the end of the third week.

These results indicate that the induction of atherosclerosis was promoted and that the regression of atherosclerosis and the decrease in hypercholesterolemia were hampered by meal eating rather than nibbling.

It was noteworthy that during the induction of atherosclerosis serum cholesterol was elevated and atherosclerosis accentuated in meal eaters in spite of a diminished total food and cholesterol intake. A true fasting serum cholesterol determination could not be done on nibbling birds so determinations were run on both groups serially during the typical day. The cholesterol concentration changed little with time of day in either meal eaters or nibblers.

During regression the birds which remained meal eaters took much longer to clear their sera of cholesterol than the nibblers. After two weeks there was a marked difference in the rate of clearing of blood cholesterol and coronary plaques between nibblers and birds continuing on two meals daily.

Birds that developed lesions while eating three meals per day showed no difference after two weeks in the rate of decrease in serum cholesterol or incidence of atherosclerosis, whether nibbling or meal eating during regression. Nevertheless, even by this time, there seemed to be less lipid in the lesions of the nibblers. By three weeks, differences between nibblers and meal eaters were definite. The authors indicate that the lesions in this case were so severe that the two week regression period was too short to reveal the difference between the two types of eating.

Other evidence of an effect of eating pattern on atherosclerosis has appeared in the literature. G. E. Cox, C. B. Taylor, L. G. Cox, and M. A. Counts (*A. M. A. Arch. Path.* **66,** *32 (1958)*), for example, found that if monkeys were fed only once daily the production of atherosclerosis was enhanced. Similarly, R. Okey, G. Scheier, and R. Reed (*J. Am. Dietet. Assn.* **36,** *441 (1960)*) showed that female rat meal eaters had higher cholesterol levels than nibblers eating the same cholesterol-enriched diet.

In a study of the effect of exercise on atherosclerosis F. F. McAllister, R. Bertsch, J. Jacobson, and G. D. Alessio (*A. M. A. Arch. Surg.* **80,** *54 (1960)*) found that after a 15 month period their exercised dogs had higher serum cholesterol levels and more atherosclerosis than nonexercised animals. They pointed out that although the unexercised animals took 24 hours to eat their food the exercised dogs finished their meal as soon as it was offered. Cohn, Pick, and Katz suggest the possibility that the difference in atherosclerosis in this dog study could be due to the fact that one group consisted of nibblers and the other of meal eaters.

Cohn, Pick, and Katz point out several possible explanations for the effect of eating patterns on atherogenesis. One is the possibility of a deficient protein intake by the meal eaters which they refute by pointing out that (a) the protein intake still exceeds the minimum daily requirement and (b) although induction is enhanced by diminished protein intake, regression is also. The second possibility is that enhanced body metabolism accompanying meal eating might stimulate cholesterologenesis. The third suggestion is that meal eating could change the lipoprotein lipase resulting in slower clearing of endogenous cholesterol.

The response of man to nibbling instead of meal eating should be carefully studied. The study by S. A. Hashim, A. Arteaga, and T. B. Van Itallie (*Lancet* **1,** *1105 (1960)*) indicates that a decrease in serum lipids results when patients change from meal eating to a formula diet fed six times daily. Eating habits may be implicated in the pathogenesis of human atherosclerosis and may help to explain some of the phenomena which are difficult to understand when only daily diet intake is considered.

ATHEROGENIC DIETS IN DIABETICS

Normal rats and alloxan-diabetic rats were fed an atherogenic diet. Hyperlipemia was greater and myocardial infarction was more extensive in the diabetic rats.

Customarily, patients with diabetes are given a diet containing relatively large quantities of fat (80 to 100 g. per day and comprising about 45 per cent of the calories). Clinicians have recognized for years that diabetic patients tend to have higher levels of cholesterol in their blood and that they are more susceptible to atherosclerotic diseases than are normal persons. These are not new considerations. In 1920 L. H. Newburgh and P. L. Marsh (*Archives Int. Med.* **26,** *647* (*1920*)) advocated diets high in fat. Periodically clinicians have suggested that excessive fat might lead to premature atherosclerosis (E. P. Joslin, *The Treatment of Diabetes Mellitus*, pp. 176 and 496, Lea and Febiger, Philadelphia (1946)).

There has been considerable debate as to whether premature atherosclerosis in diabetic patients is due to an inherited predisposition, to the altered metabolism of diabetes itself or to the diets which are commonly fed to such patients (*Nutrition Reviews* **17,** *9* (*1959*)). Some epidemiologic evdence suggests that dietary customs are more important in the genesis of diabetes as well as the incidence of its complications than is the racial background (A. M. Cohen, *Metabolism* **10,** *50* (*1961*)). This question of whether alterations in the diet of diabetics might reduce the incidence of atherosclerosis has been reviewed recently by W. H. Daughaday (*Nutrition Reviews* **17,** *289* (*1959*)).

A pertinent study in animals casts some light on this problem (N. Kalant and W. A. Harland, *Canad. Med. Assn. J.* **84,** *251* (*1961*)). These authors studied the effects of an atherogenic diet on normal and alloxan-diabetic rats. The latter had blood sugar concentrations greater than 300 mg. per 100 ml. The diet was that which had been used to induce atherosclerosis in rats (W. A. Thomas and R. M. O'Neal, *Fed. Proc.* **18,** *511* (*1959*)). Of 40 diabetic animals, ten died; of 23 normal animals two died. The remainder of the animals were sacrificed between day 170 and day 185 and samples of blood were collected for determinations of the concentrations of sugar, proteins, magnesium, lipoproteins, total lipids, and cholesterol. Gross and microscopic examinations were made of the hearts, aortas, lungs, livers, adrenals, and kidneys of each animal. Estimates were made of the per cent of atherosclerotic involvement of the aortas of each animal.

Grossly the hearts of a number of animals showed areas of myocardial necrosis. There was a yellow streaking of the myocardium and occasionally there were large firm yellow masses lying within the ventricular cavities. Microscopically there was evidence of coronary vascular disease with myocardial infarction. The yellow deposits were shown to be cholesterol containing some calcification. The aortas showed intimal streaking with fat. There was one large renal infarct in a diabetic animal. The livers were markedly enlarged due to fatty deposition and the kidneys showed minor changes.

The incidence of lesions was somewhat greater in diabetic animals than in the controls. Ten of the 30 diabetic rats showed evidence of myocardial infarction whereas three of the 24 control animals had infarction. These differences were not statistically significant. Aortic sudanophilia was of equal extent in the two groups. The concentration of cholesterol was significantly higher in diabetic animals than in the controls (2,206 versus 1,688). Similarly, values for total lipids and alpha and beta lipoproteins were higher in the diabetic than in the control animals. There were no differences in concentrations of magnesium.

These results confirm the initial report by Thomas and his group that myocardial

infarction can be induced in rats by means of diet. Furthermore, this study showed that the degree of hyperlipemia and hypercholesterolemia was higher in diabetic than in nondiabetic animals, and it suggested that the incidence of myocardial infarction was higher in the diabetic than in the control animals. The authors discussed the similarity of these vascular lesions to those which occur spontaneously in human beings. The chief difference between these animals and human beings having atherosclerotic changes was in the marked hyperlipemia of the former.

This study suggests that diabetic animals fed an atherogenic diet develop a more severe degree of hyperlipemia and atherosclerosis than do intact animals fed the same diet. Nevertheless, there are many differences between the situation encountered in diabetic patients and that which was created experimentally. Diabetic patients presumably have the benefit of a regulated diet and of the administration of insulin when necessary, whereas these factors were uncontrolled in the animals. Furthermore, the relatively small numbers of animals in this study resulted in a lack of statistical significance for the incidence of myocardial infarction.

This is a most provocative topic and one which demands meticulous investigation. It is conceivable that by proper selection of diet for diabetic patients we may in the future be able to assure a normal life expectancy and freedom from an unusual degree of atherosclerosis. At the present, however, conclusive evidence is lacking and it would be unwise to advocate drastic changes in the management of diabetic patients until sound experimental evidence has been accumulated.

ANTIOXIDANT REPLACEMENTS FOR VITAMIN E

DPPD and ethoxyquin replaced Vitamin E in rats, permitting successful reproduction, even through the second generation in the case of DPPD. Vitamin E could not be detected in the tissues of animals fed these antioxidants.

In studies on the function and metabolism of vitamin E, investigators have observed that certain antioxidants appear to exert a sparing or replacement action for vitamin E in the diet of the rat. To determine the action of these antioxidants, thereby establishing some of the mechanism of vitamin E activity, Q. E. Crider, P. Alaupovic, and B. C. Johnson (*J. Nutrition* **73,** *64 (1961)*) have investigated the extent to which antioxidants may replace vitamin E. They reported that N,N-diphenyl-*p* - phenylenediamine (DPPD) and 1,2-dihydro - 6 - ethoxy - 2,2,4 - trimethylquinoline (ethoxyquin), but not 2,6-di-*tert* - butyl - 4 - methylphenol (BHT) or ubichromanol (acid-reduced ubiquinone or coenzyme Q_{10}) will result in the birth of live young in the second reproductive cycle, when administered to rats that have been carried on a vitamin E-deficient diet and have gone through a resorption-gestation. It was possible to maintain fertility of female rats on a vitamin E-deficient diet through two generations by use of DPPD.

As a result of reproductive success in these animals deficient in Vitamin E, Crider, Alaupovic, and Johnson were particularly interested in ascertaining whether any vitamin E residue might have been transferred or been present as contamination.

To establish the presence or absence of vitamin E in the tissues of these rats they carried out a study in which they discovered that the Emmerie-Engel reagent for vitamin E gave a positive reaction. However, when separated chromatographically, they ascertained that this Emmerie-Engel reactive compound was not vitamin E. They discov-

ered that it was present in the livers of all animals on all of the diets, whether the animals received supplementary alpha tocopherol or one of the antioxidant compounds.

The chromatographic separation of the reducing substances showed clearly that animals receiving alpha tocopherol supplement had alpha tocopherol present in the liver. The various antioxidants, DPPD, ethoxyquin or BHT were readily identified in the livers of the animals receiving them. Various artifacts produced in the determination of ubichromanol prevented an evaluation of this compound.

The results of Crider, Alaupovic, and Johnson have emphasized that when either DPPD or ethoxyquin replace vitamin E in vitamin E-deficient diets, successful reproduction will occur in animals that had shown reproductive failure on a vitamin E-deficient diet. The action of these compounds is not a simple antioxidant effect, demonstrated by the fact that BHT and ubichromanol did not permit successful reproduction under the same circumstances. The ability of DPPD to carry the animals through a second generation emphasizes how successful the replacement of vitamin E by DPPD has been in the diet of the rat.

The chromatographic separations conducted by these authors have established that alpha tocopherol has been found only in the tissues of the animals to which it was administered. The antioxidants were readily identified in the tissues of the animals. The discovery by these authors of an unknown compound (called Compound X) that is present in the livers of all of the animals on these diets and the fact that this compound gives a positive reaction with the Emmerie-Engel reagent suggests the possible complexity of vitamin E metabolism in the rat. Certainly the antioxidants have provided a very useful tool which should permit the identification of metabolic mechanisms in the utilization of vitamin E.

UBIQUINONE IN VITAMIN A DEFICIENCY

The concentration of ubiquinone in the livers of vitamin A-deficient rats is increased, but there is no difference in the total amount of this substance in the livers when deficient rats were compared with supplemented controls.

In 1940 T. Moore and K. R. Rajagopal (*Biochem. J.* **34,** *335 (1940)*) observed the presence of a substance in liver which had an absorption maxima at 275 mμ. They were studying the distribution of vitamin E in various tissues by measuring its absorption at 294 mμ. To do this they restricted the intake of vitamin A so as to minimize the interference of the latter (maxima at 328 mμ) on the absorption of vitamin E. Thus, they could measure vitamin E in the depot fat without any interference, but the substance absorbing at 275 mμ prevented satisfactory measurements in the liver. The unknown substance was stable to dilute alkaline digestion, but disappeared during the saponification with concentrated alkali.

It has been only within the past ten years that a number of investigators concentrated their efforts on the substance that absorbs at 275 mμ. J. S. Lowe, R. A. Morton, and R. G. Harrison (*Nature* **172,** *716 (1953)*) reported the accumulation of two substances in the livers of vitamin A-deficient rats. Both substances had characteristic absorption spectra in the ultraviolet. One of the substances with a peak at 275 mμ was called SA and was later designated ubiquinone. A deficiency of vitamin A produced a sharp increase in the concentration of ubiquinone in the livers of rats (F. W. Heaton, Lowe, and Morton, *Biochem. J.* **67,** *208 (1957)*). To determine whether the apparent accumulation of ubiquinone in the livers of rats

deficient in vitamin A was directly related to the deficiency state, Lowe *et al.* (*Ibid.* **67,** *215* (*1957*)) further examined chicks and guinea pigs. In neither one of these species was there any increase in the concentration of ubiquinone in the livers of vitamin A-deficient animals.

To study the influence of the vitamin A deficiency on the concentration of ubiquinone in the livers, Morton and W. E. J. Phillips (*Biochem. J.* **73,** *416* (*1959*)) placed weanling rats on a semi-purified diet deficient in vitamin A. The food consumption of the rats on the deficient diet increased steadily from 5 to 6 g. per day at the start of the study to a maximum of about 9 g. at the eleventh to thirteenth day. After that, the food intake decreased, whereas body weight continued to increase for a few days. Some rats did not stop growing until about the twenty-seventh day; their food consumption began to fall off four days before the maximum body weight was attained. Where the animals were maintained on the deficient diet until a marked loss in body weight occurred, food consumption was reduced but not excessively (no data presented on this point).

The slight reduction in food intake by the vitamin A-deficient rats might be due to an alteration in the "satiety center" in the hypothalamus. R. C. Agnew and J. Mayer (*Nature* **177,** *1235* (*1956*)) found that when this center was destroyed in vitamin A-deficient rats that had reached a weight plateau, they began to eat more of the deficient diet and to show weight increases of 70 to 200 g.

The concentration of ubiquinone in the livers of the vitamin A-deficient rats (Morton and Phillips, *loc. cit.*) increased steadily from a level of 82 μg per gram after five days on the deficient diet to 300μg when body weight gain ceased. Then, as the animal lost weight, there was a further increase to 400 μg. From the data presented in the tables, it is possible to calculate the total amount of ubiquinone in the livers of these animals. The total amount of ubiquinone in the liver increased from 308 μg on the fifth day of the deficient diet to 962 μg on the twentieth day.

As an extension of the above work, Phillips and Morton (*Biochem. J.* **73,** *430* (*1959*)) removed the adrenals from young rats that had been kept on the vitamin A-deficient diet for 45 days. During the subsequent 43 hours they were offered 0.7 per cent sodium chloride solution in place of water. These animals, weighing 81 g., had no detectable vitamin A in their livers. The concentration of ubiquinone was 511 μg per gram in the unoperated animals and 397 μg in the adrenalectomized ones. The entire liver in these two groups contained 1,845 and 1,425 μg, respectively.

Another group of rats was kept on the vitamin A-deficient diet for 33 days at which time each rat weighed approximately 100 g. and had reached a plateau. At that time, five male and five female rats were adrenalectomized. For 72 hours thereafter they were maintained on the deficient ration and the saline solution. Again, vitamin A could not be detected in the liver. There was no sex difference in the ubiquinone concentration in the livers (222 μg and 212 μg per gram for the male and female controls and 356 and 365 μg per gram for the adrenalectomized rats). The slight difference in the liver concentration of the controls and adrenalectomized rats is not significant. There is an even greater similarity in the ubiquinone contents of the entire livers: for the male and female control rats, the values were 1,050 and 1,034 μg, respectively, and for the adrenalectomized rats, the values were 1,278 and 1,420 μg.

Adrenalectomy of rats maintained on a stock diet for 57 days and then kept for an additional ten days on saline also produced no change in the ubiquinone content of the livers (Phillips and Morton, *Biochem. J.* **73,** *430* (*1959*)). The control rats had 1,408

and 1,045 μg per whole liver for the males and females, while the adrenalectomized rats had 1,062 and 867 μg, respectively.

In the preceding study, the adrenals were examined since there had been reports of histological changes and biochemical alterations in this gland in vitamin A-deficient rats. The latter report was based primarily on the conclusion of G. Wolf and co-workers (*Nutrition Reviews* **17,** *47* (*1959*)) that a vitamin A deficiency interferes with the synthesis of glucocorticoid hormones.

Moore and I. M. Sharman (*Brit. J. Nutrition* **14,** *473* (*1960*)) criticized the above work which indicated an increase in the ubiquinone concentration of the livers of vitamin A-deficient rats. They felt that the analytical method used by Morton and his co-workers for ubiquinone was not properly standardized in that varying amounts of tissue appeared to have been examined by processes which probably varied in the digestion time and the volumes of solvents used for chromatography. They claimed that special attention must be given to these points to prevent destruction of the relatively labile ubiquinone.

To overcome these objections, Moore and Sharman omitted chromatography from their method since they felt that this procedure had not been studied sufficiently to evaluate its effect on the stability of ubiquinone. They digested their tissue samples for three minutes with 60 per cent KOH and extracted the digest with diethyl ether. After evaporation of the solvent, the residue was taken up in cyclohexane. The absorption curves secured for the latter agreed with that of pure ubiquinone when the concentration of vitamin A in the tissue was low. When large amounts of vitamin A were present, a correction was applied to the absorption curve based on the absorption maxima for vitamin A at 328 mμ.

Weanling rats were put on a semi-purified diet deficient in vitamin A (Moore and Sharman, *loc. cit.*). Eight animals in one group were maintained on this ration, while each of the other eight rats in the other group received 40 I.U. of vitamin A acetate per week. After 49 to 62 days on the deficient diet, the concentration of ubiquinone in the livers of the rats averaged 520 μg per gram, while the livers of the supplemented rats sacrificed at the same time as the deficient rats had 340 μg per gram. The whole livers of the deficient rats had 3,300 μg while the livers of the supplemented rats had 3,800 μg. The deficient rats had ceased to grow or showed signs of hematuria or xerophthalmia when they were sacrificed. They weighed 179 g. at that time, while the supplemented rats weighed 248 g. These observations suggest that the concentration of ubiquinone in the smaller livers of the vitamin A-deficient rats is increased, but there is no change in the total amount present.

The heart normally has a very small amount of vitamin A; consequently there is no problem associated with absorption interference of the latter. Both the concentration and the total amount of ubiquinone in the hearts of the vitamin A-deficient and supplemented rats were the same (520 μg and 300 μg per gram per heart, respectively).

Results similar to the above were secured with another group of ten deficient rats and the same number supplemented with 1,000 I.U. of vitamin A acetate per week.

On the basis of theoretical corrections in the absorption coefficient for ubiquinone and vitamin A at 275 and 238 mμ, Moore and Sharman (*loc. cit.*) concluded that there was actually a slight increase in the total amount of ubiquinone in the livers of the vitamin A-deficient rats. These corrections did not apply to the heart.

The results of both groups of investigators agree in showing an increase in the concentration of ubiquinone as a vitamin A deficiency progresses in the rat. The agreement occurred in spite of the fact that different procedures were used in evaluating the concentration of ubiquinone. Although

there are differences in the level of ubiquinone reported by the two schools, they differ only by a factor of two or three, and that may be due to strain, dietary differences or analytical procedures.

There is still some question as to whether the actual amount of ubiquinone in the liver increases in vitamin A deficiency or whether the loss of liver tissue experienced by these animals only concentrates the ubiquinone. It is doubtful whether the latter explains the situation, since the deficient rats never weighed as much as the controls. In view of the similarity of the ubiquinone content in the livers of the deficient and the control rats, one might wonder whether the rat synthesizes this substance at a constant rate which is independent of growth or other factors. Should this be so, it would be desirable to determine the age of the rat when the liver has accumulated its maximum amount of ubiquinone. There is a possibility that this stage might be a means of determining when physiological or biochemical maturity has occurred.

The above studies indicate that the concentration of ubiquinone is increased in the livers of vitamin A-deficient rats, but is not increased in guinea pigs or chicks. There is, however, only a slight increase, if any, in the total amount of ubiquinone in the livers of the vitamin A-deficient rat. There is no difference either in the concentration or the total content of ubiquinone in the heart of a vitamin A-deficient rat. Adrenalectomy has no influence on either the concentration or content of ubiquinone in both vitamin A-deficient and supplemented rats. Further work by Morton and Phillips (*Biochem. J.* **73,** *427 (1959)*) indicates that a deficiency of vitamin E has no effect on the levels of ubiquinone in the livers of rats. The significance of the increase in the concentration of ubiquinone in the livers of vitamin A-deficient rats is unknown.

PHYSICAL ACTIVITY AND MYOCARDIAL INFARCTION

Rabbits made atherosclerotic by feeding an atherogenic diet were found to be abnormally susceptible to myocardial infarction when subjected to strenuous exercise or given injections of thrombin or pituitrin.

In searching for evidence that would explain the high incidence of myocardial infarction in the Western world, clinicians have considered many factors. A reasonable view seems to indicate that heredity, diet, state of nutrition, smoking habits, emotional state, and amount of exercise are all significant factors (J. Yudkin, *Archives Int. Med.* **104,** *681 (1959)*). Animal experiments designed to evaluate any protection that exercise may provide against atherosclerosis have been reviewed recently and seem to indicate that exercise exerts some beneficial effect (*Nutrition Reviews* **19,** *55 (1961)*).

A group of Russian investigators reported recently on an experiment designed to evaluate the effects of (a) myocardial stress (severe exercise), (b) hypercoagulability of the blood, and (c) spasm of the coronary arteries on the incidence of myocardial infarction in rabbits made atherosclerotic by diet (A. L. Myasnikov, N. N. Kipschidze, and E. I. Tchazov, *Am. Heart J.* **61,** *76 (1961)*). Rabbits were fed an atherogenic diet according to the method of N. Anitschkow (*Beitr. z. path. Anat. u. z. allg. Pathol.* **56,** *379 (1913)*). Twenty-two animals were fed this diet alone, and none of these developed myocardial infarcts. Another 25 were fed the diet for 180 days and were exercised severely for one hour daily throughout the experiment. These animals were kept on a treadmill during the exercise period until many of them became severely dyspneic at intervals throughout the study. All of these animals developed myocardial

infarcts. Eight rabbits were exercised, but were fed a normal diet. None of these had myocardial infarcts.

Another group of 15 rabbits was fed the atherogenic diet for 120 days, then given a single intravenous injection of thrombin. Ten of these developed myocardial infarcts. However, eight healthy rabbits similarly injected did not develop infarction. Similarly, an intravenous injection of 0.3 to 0.5 cc. of pituitrin (to induce coronary spasm) did not induce infarction in ten healthy rabbits. However, combined administration of pituitrin and thrombin to 21 healthy rabbits resulted in myocardial infarction in 17 of them.

Finally the authors fed the atherogenic diet to 16 rabbits for only 70 days, then gave injections of pituitrin and thrombin and found that 14 of these developed myocardial infarcts. They concluded that coronary atherosclerosis was the most important factor but that exhaustive exercise, hypercoagulability of the blood or coronary spasm provided additional insults which served to precipitate acute myocardial infarctions.

This report seems to be based upon valid observations, but would have been better if determinations of blood coagulability had been made. Also, one wonders about the final weight of the exercised animals and their caloric intake as compared with control animals. This report does not provide any estimate of the effects of graded exercise upon the incidence of coronary occlusion. Therefore, previous reports do not conflict with this one since the methods employed were entirely different. The results of this study suggest that a heart already hampered by coronary sclerosis is less apt to withstand the insults which might be inflicted by disease or environment.

NOTES

A Hypothalamic Fat Center

Hypothalamic centers are postulated or demonstrated for a number of functions, including appetite (*Nutrition Reviews* **11,** *55 (1953)*; **16,** *7 (1958)*) and thirst (*Ibid.* **16,** *302 (1958)*). Still others affect carbohydrate metabolism in complex ways. This reviewed work implicates a localized hypothalamic area in the regulation of blood fat levels.

G. Murray (*Am. J. Surg.* **700,** *676 (1960)*) observed two patients who died with fat embolism without injury. Fat embolism is generally ascribed to circulating fat globules originating at the site of bone fractures or crushing injuries of adipose tissue. The lesion is not observed in routine autopsy sections as these are ordinarily defatted. Thus its presence in uninjured patients is not usually sought.

One of Murray's patients had anaphylactic shock and died in renal insufficiency a week later. Fat embolism was widespread. The other patient is not described.

Murray sought to produce fat embolism without traumatizing adipose tissue. Interested in Claude Bernard's demonstration of a "diabetic center" in the floor of the fourth ventricle, he repeated the "piqûre" experiments in rabbits in the hope of finding a similar center affecting fat metabolism.

A number of graphs are reproduced showing the resulting changes in blood sugar and blood lipids. In order to avoid influencing the "diabetic center" Murray changed to a parietal approach, exposing the inferior surface of the brain. By exploring with the needle he found an area, "the stimulation of which gave a sharp rise in blood fat," located "2 mm. above the inferior surface of the hypothalamus and mid-way between the optic chiasma in front and the stalk of the pituitary behind. A more anteriorly located area significantly gave a drop in blood fat." A total of 150 experiments were performed on rabbits and 29 on dogs, with similar results in the two species.

The author infers that there is a fat center in the hypothalamus which influences the blood fat level. The paper does not establish the conclusions sufficiently for the critical reader. There are no bibliographic references and no adequate description of the chemical methods used. The determinations shown in a number of graphs are all after craniotomy; no pre-craniotomy controls are given. Most of the 11 graphs (based on various sites of needling) show irregular changes. However, at least one graph shows a striking rise in plasma lipids from about 300 mg. per 100 ml. just before piqûre to about 800 mg. per 100 ml. four hours later. The blood sugar rose from 200 mg. per 100 ml. to 300 mg. per 100 ml. in the same period. The anesthetic agent is not stated.

Although Murray's paper does not document his experiments sufficiently in many respects, the concept of a hypothalamic locus affecting blood lipid or fat is sufficiently important that a more critical repetition of the work is desirable to prove or disprove the thesis.

However, the idea of a "fat center" is by no means a simple one. If one can reason by analogy with the hypothalamic and medullary centers affecting blood glucose levels, one will then have to look for nerve-mediated effects on organs, *e.g.* livers, adrenals and adipose tissue; humoral factors released from the hypothalamus; and interrelationships with the pituitary, including various lipid-mobilizing factors of the pituitary and other glands (*Nutrition Reviews* **18,** *347* (*1960*)).

Vitamin B_6 Content of Infant Foods

Several years ago it was observed that infants whose diets were deficient in vitamin B_6 developed symptoms of irritability and convulsions. Cure was rapid when vitamin intake was increased. Detailed study of such infants led O. A. Bessey *et al.* (*Pediatrics* **20,** *33* (*1957*)) to conclude that 0.2 to 0.3 mg. daily is the vitamin B_6 requirement for young infants.

A recent paper concerns the vitamin B_6 content of a number of milk products and solid foods commonly used in infant feeding. N. A. Hurley and R. A. Stewart (*Pediatrics* **26,** *679* (*1960*)) report the results of assays of some 95 samples of milk and milk substitutes, and of 81 samples of commercially prepared infant foods. Assays were done microbiologically using *Saccharomyces carlsbergenesis* as the test organism. The results were expressed merely as mg. "vitamin B_6," or per cent estimated daily requirement (0.25 mg.) of same.

It is of interest that the microbiological assay method yields low results in comparison to assays based on the growth of young rats (*Nutrition Reviews* **13,** *342* (*1955*)).

The milk and milk substitutes were obtained from retail stores; the other foods were obtained from the production plants of a baby food manufacturer. Three widely separated areas of the country were represented. Food samples had been prepared six to 24 months prior to time of assay.

Pasteurized cow's milk was found to contain 0.19 mg. vitamin B_6 per 100 ml., commercially prepared soybean base formulas 0.11 mg., and a "meat base" formula 0.07 mg. (The latter product is one designed for infants who do not tolerate milk—various meats supply the protein moiety.) Evaporated milk contained 0.06 mg. per 100 ml., and the contents of four different prepared cow's milk formulas (which are unfortunately identified only by code number) varied from 0.06 to 0.08 mg. per 100 ml.

It is unfortunate that the authors do not compare the results of their assays with those reported by other workers. For instance, the Report of the Committee on Nutrition of the American Academy of Pediatrics (*Pediatrics* **26,** *1039* (*1960*)) lists cow's milk as containing 0.05 mg. per 100 ml., or one-quarter as much as that found by Hurley and Stewart. Furthermore, the range of variation for individual foods is not given, while other sources of data,

such as the *Heinz Handbook of Nutrition* (*McGraw-Hill, New York (1959)*), do so. This source lists cow's milk, for example, as containing 0.05 to 0.11 mg. per 100 ml.

The daily consumption of a quart of these formulas would thus provide the infant, according to Hurley and Stewart, with from 190 to 340 per cent of the estimated daily requirement. By way of comparison, a quart of human milk contains only 0.11 mg. vitamin B_6, or about one half of the estimated requirement (*Pediatrics* **26,** *1039 (1960)*; *Nutrition Reviews* **18,** *136 (1960)*). This amount can be increased by giving pyridoxine to the mother.

The various solid foods are separated into a number of categories. Meat and cereal products are the richest sources of the vitamin. Beef liver had the highest content (0.8 mg. per 100 gm.) of any food assayed. Other meat products ranged from 0.2 to 0.5 mg. per 100 gm., and the various cereals from 0.3 to 0.5 mg. Egg yolks contained 0.2 mg. per 100 gm., and strained vegetables ranged from 0.04 to 0.1 mg. (sweet potatoes were the highest). Strained fruits contained 0.02 to 0.15 mg. per 100 gm., with bananas at the top of the list. Fruit juices had 0.03 mg., infant desserts 0.03 to 0.15, and mixed meat and vegetable products 0.05 to 0.2 mg. per 100 gm.

No appreciable differences were found to be due to the geographic area in which the foods were grown and packed. The authors have also calculated results in terms of 100 calorie units.

It is apparent that normal infants consuming the usual diet of milk or milk substitutes and commercially prepared infant foods receive an abundant supply of vitamin B_6.

Recent Books

Survey of Dentistry. Final report of the Commission on the Survey of Dentistry in the United States. Byron S. Hollinshead, Director. Published by American Council on Education, Washington, D. C. Pp. 584. Price $10.00.

Pure Food and Pure Food Legislation. Editor, A. J. Amos. Published by Butterworths, 7235 Wisconsin Avenue, Washington 14, D.C. and London, England. Pp. 167. Price $4.00.

The World Food Deficit—A First Approximation. Foreign Agricultural Service, U. S. Department of Agriculture, Washington 25, D.C.

Performance Capacity. A Symposium. Edited by Harry Spector, Josef Brožek and Martin S. Peterson. Advisory Board on Quartermaster Research and Development. Committee on Foods, National Academy of Sciences-National Research Council. Pp. 257.

Toward the Conquest of Beriberi. By Robert R. Williams. Published by Harvard University Press, Cambridge, Massachusetts. Pp. 338. Price $7.50.

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